Immunodeficient Rodents Opening New Doors For Investigators (cont.)

Immunodeficiency Mutations In Mice

Single-gene mouse mutants have provided highly useful experimental research models, notably the nude mouse (reported in 1966) and the scid (discovered in 1980).

More than 4,000 genes of the mouse have now been assigned to specific chromosomal locations. Many genes were first identified following spontaneous mutations that produced distinctive physical characteristics. Single-gene mouse mutants have provided highly useful experimental research models. Two key single-gene, naturally occurring mutations are the nude *(nu)* and the severe combined immunodeficiency *(scid)*; both are important research models for the study of xenografts, transplanted tissues and tumors from foreign species. Other single-gene mutations commonly used as research models include the beige (bg) and the X-linked immune deficiency (xid).

The nu mutation was first reported in 1966 in a closed stock of mice in a laboratory in Glasgow, Scotland. It was not until 1968, however, that it was discovered that the homozygous nude mouse also lacked a functional thymus, i.e., it was athymic. The mutation produces a hairless state, generating the name "nude." The other, unique defect of nude mice is the failure of the thymus to develop normally to maturity. The thymus remains rudimentary and produces reduced numbers of mature T cells. This means nude homozygotes (animals with identical mutant genes at corresponding chromosome loci) do not reject allografts and often do not reject xenografts (tissue from another species). The discovery that human neoplasms (tumors) could be grown in nude mice was immediately recognized as an important research tool. Thus, the spontaneous mutation of *nu* among laboratory mice was a serendipitous development that led to the nude mouse becoming the first animal model of a severe immunodeficiency. In the decades since, the nude mouse has been widely utilized by researchers studying factors regulating transplantable human tumor growth and cancer metastasis.

Although it lacks T cells, the nude mouse has a normal complement of bone-marow-dependent B cells. It thus presented a unique tool for the study of the role of the thymus on lymphocyte differentiation, investigations of B cell functions (including interactions with other immune cells) and studies of the actions of other immune cells, including the natural killer (NK) cells. Nude mice have elevated levels of both macrophages and NK cells; their macrophages are more potent than those from mice with a normal thymus.

The first successful transplantation of a human malignant tumor to nude mice was reported in 1969. Nude mice have been used extensively in studies of the tumorgenecity of *in vitro* cultured cells. Nude mice are also widely utilized in evaluating anticancer agents
prior to human clinical trials.

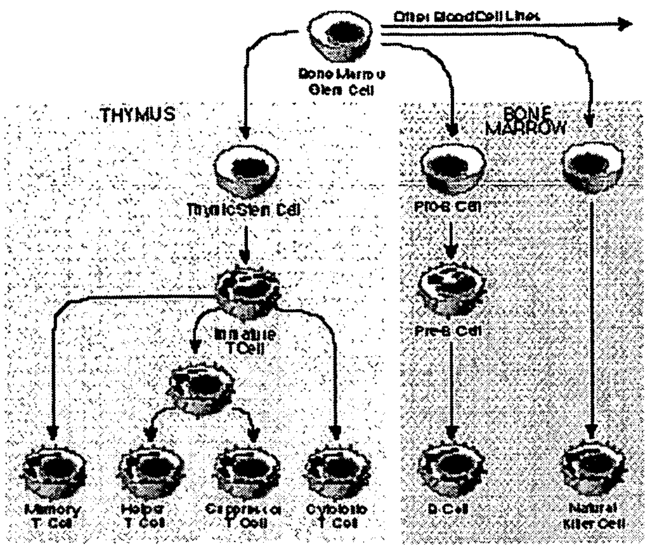

Figure 1. Lymphocytes differentiate from bone marrow stem cells. Those that mature in the bone marrow become B cells or NK cells; those that migrate to the thymus and mature there become T cells. Breakdowns in critical sectors of the differentiation process are believed to result in various immunodeficiency disorders, including scid.

SCID Mice: Accident of Nature

Serendipity also played a role in the discovery of another important mutant strain of immunodeficient mice, which lacks both B and T cells, called severe combined immunodeficiency (scid*)* mice. During routine lab tests on the immune system in mice, Dr. Melvin J. Bosma of the Fox Chase Cancer Center in Philadelphia discovered the strain in 1980.[2] The first scid mice were an accident of nature, the product of chance matings of apparently normal mice that carried a recessive mutant gene now called scid. Some of the offspring inherited a complete pair of scid genes and were born with the scid defect.

"We were conducting antibody studies when we found that some of these mice lacked antibody," recalls Dr. Bosma. "The disease seemed to affect cellular immunity, too. These animals had tiny lymph nodes and the thymus was about one-tenth normal size. It took about 3 years to determine and demonstrate that these mice had a severe immune deficiency disease similar to that called SCID that afflicts some human children."

Dr. Bosma's laboratory bred these mice with each other to produce the original scid colony. At first, the scid mouse attracted interest because it was the first known animal model for human SCID, a congenital syndrome that is usually fatal to human babies. The scid mouse is also an excellent model for studying the relationship between immune defects and cancers of the lymph system. The Fox Chase researchers found that histologic abnormalities in scid were remarkably uniform, because they all share the same underlying genetic defect.[3] Dr. Bosma and his colleagues also noted that, like

nude mice, the normal immune function of scid mice could be genetically reconstituted by "seeding" with lymophocytes from bone marrow of normal mice. But because the scid model lacks both B and T cells, it presents much greater potential for studies of selective reconstitution of immune cell populations.

The action of the *scid* mutation in blocking lymphocyte development is not absolute, however. As they mature, some adult scid mice generate a few clones of functional B and T cells. These scid mice are said to be "leaky," meaning that low levels of B and T cells are detectable. "By 10 to 14 months of age, virtually all [C.B-17] scid mice are leaky," says Dr. Bosma. "Those with detectable B cells also invariably contain T cells. This implies that the development and growth in numbers of B cells in scid mice may be totally dependent on T cells andperhapsvice versa."

However, other researchers now report that another strain of scid mice appears to be virtually devoid of the leaky phenotype. (See 'Leakiness' in C.B-17 SCID vs. ICR SCID, Page 5.)

Click here to go to page 3